



A Report on *Alzheimer's Disease* and Current Research

by Dr. Jack Diamond, Scientific Director
Alzheimer Society of Canada

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Dr. Diamond received his PhD and subsequently his medical degree at the University of London, England, after which he did two years of post-doctoral research at Harvard Medical School, returning to a faculty position at University College London. He is widely published, having written more than 70 papers in refereed journals, and 15 book chapters.

The Alzheimer Society

The Alzheimer Society is a nationwide, not-for-profit health organization dedicated to helping people affected by Alzheimer's disease. The Society consists of a national office, 10 provincial organizations and more than 140 local offices across the country. The Society develops and provides support and educational programs and information for people with the disease, their families, caregivers and members of the health-care team. The Society is a leading funder of Alzheimer research in Canada.

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Introduction

For the past few years Dr. Jack Diamond has been making presentations on Alzheimer's disease research to various audiences across Canada and internationally. From these presentations, *A Report on Alzheimer's Disease and Current Research* has been created. The purpose of this report is to provide people outside of the scientific community with easy to understand information on Alzheimer's disease, the known risk factors, the most recent research into new treatments and the search for a cure. Essentially, the report was generated in response to questions from non-specialists about biomedical issues in the field of Alzheimer research. Given the importance of Social/Psychological research, this report also mentions some of the issues Socio-Psychological researchers address to help improve the quality of life for people with Alzheimer's disease, their caregivers and their families. To keep pace with the rapid advances in research, this report is updated periodically.



What is Alzheimer's disease?

Alzheimer's disease is the most widespread of a large class of disorders which clinically are known as "dementias". It is a disease of the brain, characterized by a progressive deterioration of thinking ability and of memory. Within the brain itself nerve cells die because of a number of abnormal ("pathological") events, the principal ones being the development of the "plaques and tangles" that Dr. Alzheimer first described a hundred years ago.

The disease progresses slowly. Forgetfulness gradually increases, and in the later stages even close family members may fail to be recognized. The ability to carry out normal activities such as reading, driving, and cooking gradually decreases, as does the ability to make judgments and appropriate responses to everyday issues. There can also be behavioural changes such as agitation, aggression, depression, disturbances of balance and movement, and an inability for people to find the way even in familiar surroundings. In time the affected person becomes unable to look after themselves and caregivers are required. Alzheimer's disease is ultimately fatal; and although there are some exceptions, death usually occurs within seven to 10 years after diagnosis.

It is important to know that Alzheimer's disease is not a normal part of aging. The decline in memory, and in thinking ability reflect the progressive death of brain cells caused by the disease process. This is quite different from

relatively minor brain cell loss that may occur naturally with aging.

While one out of every 20 Canadians over the age of 65 has Alzheimer's disease, that number rises to an alarming one in four of those over 85. The majority of these cases are of the "sporadic" or "late onset" form of Alzheimer's disease, implying that the disease has no specific family link. However, about seven per cent of the Alzheimer population are in the category called "Familial" Alzheimer's disease (FAD), or "early onset" Alzheimer's disease. FAD is identical to the sporadic form, but it is largely attributable to the inheritance of certain genes which at some point in that family tree "mutated", that is they changed their normal character to an abnormal one, in consequence making entire families susceptible to Alzheimer's disease.

New diagnostic approaches which are detecting Alzheimer's disease at earlier stages, the addition of the "baby boom" numbers to the aging population, and the increasing incidence of the risk factors for Alzheimer's disease (described on page 2), are causing a striking increase in the number of younger people who are being diagnosed with the disease. While this makes it appear as though a new type of "early onset" Alzheimer's disease is appearing, this is not the case. The disease has not changed its character, it is simply being detected earlier, and in greater numbers.

How is Alzheimer's disease diagnosed?

Alzheimer's disease was originally regarded as a purely behavioral disorder, but this changed when Dr. Alois Alzheimer showed 100 years ago that there were also specific abnormalities in the brain. He examined brain tissue from his patient who had just died with dementia and observed the plaques and tangles (these are described later) which are now accepted as the hallmarks of the disease. It is these distinguishing abnormal features that prove Alzheimer's disease but unfortunately this can only be done post mortem. Today doctors use many methods to assist them to make a diagnosis. They first start by eliminating other known diseases that can cause dementia, such as Parkinson's disease. After that comes a battery of psychological and memory tests which are fairly accurate (90-95%) in allowing a diagnosis of Alzheimer's disease to be made. Today the accuracy of diagnosis is improved by the increasing use of "CAT scans" and brain imaging techniques such as Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET). In some countries genetic testing for the presence of the "apoE4" gene, an important risk factor for Alzheimer's disease (apoE4 is described later) is also contributing to the accuracy and rapidity of diagnosis, although genetic testing is not yet accepted as a routine procedure in Canada.

It was recently reported that the steady weight loss normally associated with aging doubles in the year before even the mildest Alzheimer-like symptoms become evident. This in itself would make only a minor contribution to diagnosis, but it suggests the possibility of Alzheimer-related processes that affect the body even earlier than they do behaviours. Researchers are continually looking at persons in the earliest stages of Alzheimer's disease for unusual changes in easily examined tissues like the skin, blood, and cerebrospinal fluid. The aim is to find simple tests for early diagnosis, and some success is occurring here (see "The Next Ten Years", page 13).



What causes Alzheimer's disease?

It's often stated that we don't know what causes Alzheimer's disease, but many are coming to the conclusion that in a sense we actually do. All the organs of the body, including the brain, have built-in self-repair mechanisms. Alzheimer's disease appears to develop when the combined effects of the known and still to be identified influences called "risk factors" cross a certain "threshold". At this point they overwhelm the natural self-repair and self-healing mechanisms in the brain that normally maintain the nerve cells in a healthy state.

Risk Factors:

These are characteristics of the person and the person's life-style and environment that contribute to the likelihood of getting the disease. While most risk factors are well established, some are still controversial. Many of the risk factors for Alzheimer's disease, like high cholesterol levels or high blood pressure or having the apoE4 gene, are risk factors for many other diseases as well.

Aging: this is the most important risk factor. Whatever other risk factors are present, including the genetic ones discussed next. Alzheimer's disease never sets in until some minimum adult age is reached. An important consequence of aging is deterioration in the efficiency of the body's self-repair mechanisms. The deterioration occurs at different rates in different people, which may also explain in part why some people are more susceptible to getting Alzheimer's disease than others. At first sight aging would appear to be the one risk factor that we can do least about. Surprisingly, this may not be so. A huge amount of research is going into finding out what causes the progressive deterioration in aging of tissues and organs that include the brain, and there is a genuine feeling that the answer is not beyond reach. There is solid evidence that in animals a rigorously controlled caloric restricted diet (CR), beginning at weaning, dramatically slows the aging process, but instituting an equivalent life-long CR in humans is just not possible. However, the fact that body aging can be influenced at all is a very important stimulus to scientific research on aging. The objective is not so much to prolong life as to prevent the slow decline in function. Everybody knows that some older people seem to have remarkably young brains, while by contrast, others seem to be "old

before their time". The point here is that from the perspective of Alzheimer's disease, it is not chronological age that matters but brain age, something we can recognize but so far cannot control. One encouraging item is that scientists are well on their way to understanding the brain's self-repair mechanisms, and are looking at ways to activate them when they seem to be "switching off", as in aging.

Genetic risk factors: aside from the mutated genes responsible for FAD mentioned earlier, the most important genetic risk factor for both the familial and the sporadic forms of Alzheimer's disease is the apoE4 gene. This gene is not, however, an abnormal one, i.e. it has not undergone a mutation that has impaired its ability to carry out its usual job. ApoE4 is one of the three variants of the apoE gene, the others being the benign apoE2 and apoE3 genes. Everybody has a double set of genes, one from each parent. If a person's pair of apoE genes include one apoE4, they have three times the normal risk of developing Alzheimer's disease, but if they carry two apoE4 genes the risk increases to ten times. That said, it is also important to note that people with no apoE4 genes can still get Alzheimer's disease, and people with two apoE4 genes can escape it.

Researchers are actively looking for evidence of other quite normal genes that predispose one to Alzheimer's disease, but it seems unlikely that these still to be discovered genes will be as important a risk as the apoE4 one. Normal genes that predispose the carrier to certain diseases are becoming increasingly recognized, especially in cancer research. Although the genes and those responsible for FAD are there from birth, they can't cause the disease on their own; the brain has to reach a certain critical age, significantly younger for FAD than for sporadic Alzheimer's disease, but still well into adulthood. So the age requirement applies to the genetic risk factors as for the other more general risk factors now to be itemized.

In addition to aging and to genetic factors, all the following have been documented as risk factors for Alzheimer's disease. Unfortunately, many of them tend to increase with increasing age.

- diabetes - it has been known for some years that type 2 (adult) diabetes is a risk factor for Alzheimer's disease, in large part, it was assumed, because of the associated blood vessel and heart disorders, and sometimes obesity, that are



known risk factors for Alzheimer's disease. It's also well established that glucose utilization is impaired in the brains of people with Alzheimer's disease, rather like the situation in the bodies of people with diabetes. New research techniques and brain imaging have now revealed that the impairment in the Alzheimer brain is probably because the brain is itself in a sort of diabetic state, even though the person may not be diabetic in the ordinary sense. It seems that in the brain either (i) the production of insulin (known to occur in brains) is reduced for some reason, in this regard resembling type 1 (juvenile) diabetes, in which the insulin-producing cells of the pancreas are destroyed, or (ii) that the brain cells are becoming insensitive to insulin, like the rest of the body's cells in type 2 diabetes, in which insulin is produced in the pancreas in quantities even greater than in normal individuals, but it doesn't work. The outcome of these discoveries is that new anti-diabetic drugs which help people with type 2 diabetes respond to insulin, are now being tested to find out if they can reduce the abnormalities in the brains of people with Alzheimer's disease who are not diabetic. There are promising indications of memory and cognitive improvement in these people.

- family history - having a parent or sibling with Alzheimer's disease increases the risk two to three times, implying the likely involvement of genes not yet identified.
- Mild Cognitive Impairment (MCI) – this important condition is discussed later (see page 9).
- the post-menopausal state in women - twice as many women get Alzheimer's disease than men; this is partly explained by their living longer than men on average, partly because women are more prone than men to get diabetes, itself a risk factor, but in large part because in post-menopausal women there is a decline of the important hormone estrogen.
- Down's Syndrome - almost all with this disorder who survive into their 40s will develop Alzheimer's disease.
- chronic inflammatory conditions, such as certain forms of arthritis.
- a history of episodes of clinical depression.
- head injury, also known as “traumatic brain injury”, or TBI.
- strokes or “ministrokes”; the latter are very small hemorrhages in the brain that seemed not to have caused any symptoms when they occurred, but evidence that they did indeed occur is clearly visible when routine brain imaging is done at later times.
- high cholesterol levels.
- high blood pressure.
- stress.
- lack of physical exercise.
- inadequate exercising of the brain - in a twin study, the ones doing more intellectually demanding work were less likely to develop the disease than their identical twins.
- “unhealthy” eating habits.
- obesity.
- low levels of formal education.
- low socio-economic status (this – like the low levels of education risk, may reflect the existence of other of the listed risk factors in persons in these categories).

There are also risk factors that are not so firmly established such as smoking, excessive drinking, and taking drugs of abuse. Researchers are still examining whether some people are at risk because their bodies have difficulties in handling foods containing the metals copper, iron, and aluminum, although most researchers no longer regard aluminum as a risk factor for Alzheimer's disease.

Always remember, however, that exposure to any or even to all of the known risk factors does not mean that a person will get Alzheimer's disease. Equally one may have limited exposure to the known risk factors and yet still develop the disease.

How can we reduce the risk of developing Alzheimer's disease?

Only the genetic risk factors and aging are currently beyond our control. It's important to understand that what matters is not only how many risk factors a person might be exposed to, but as already mentioned, how efficiently the self-healing processes in his or her brain operate. It seems that the brain's ability to withstand risk factors and to preserve and even enhance its healing capacity can be enormously helped by adopting appropriate healthy lifestyles. These actually promote the ability of brain cells to maintain connections with each other and make new connections. Recent discoveries suggest that healthy lifestyles may even help in the creation of new nerve cells, which is discussed later in the context of brain repair. The importance of lifestyle can be appreciated from studies of identical twins, who share the same genes. It turns out that about 60% of the overall risk factor for Alzheimer's disease comes from lifestyle and not genetic susceptibility. Healthy lifestyles also reduce specific risk factors such as stress and obesity. Of obvious benefit are practices such as the wearing of safety helmets to reduce traumatic head injury, and the appropriate treatment of medical conditions such as diabetes and high cholesterol levels.



Things that may help reduce the risk of Alzheimer's disease, or even slow the disease progress once it has begun include:

- **healthy eating** - the focus here is on a "Mediterranean" type diet and on eating "anti-oxidant" - rich foods such as blueberries and raspberries, and dark green leafy vegetables such as spinach and collard greens ("free oxygen radicals" – oxidants - are potentially dangerous products of metabolism which are normally disposed of by the body's own anti-oxidants). Also recommended by some are the anti-oxidants selenium and folic acid (folic acid, also called folates, is reputed also to help ward off heart disease; it occurs in a wide variety of foods ranging from liver and fruits to whole wheat bread and lima beans, but like vitamin C is destroyed by cooking or processing). Recently a beneficial effect of fruit and vegetable juices was reported (at least three glasses weekly) that appeared to be more related to the presence in the juices of antioxidants called polyphenols rather than the presence of the antioxidant vitamins such as E or C (vitamin E supplementation is controversial because of a recent report that such supplementation is a potential health hazard). Finally, there is a new interest in increasing one's intake of omega-3 fatty acids, found especially in cold water fish, flax and walnuts, after findings that these fatty acids were low in people with Alzheimer's disease, and that in some studies their dietary supplementation improved cognitive functioning.
- **caloric restriction** - in mouse models of Alzheimer's disease it's been discovered that rearing them on a reduced calorie diet substantially decreased the accumulation of amyloid plaques. For people, it is important to maintain a healthy weight.
- **aerobic exercising** - even the most modest levels are beneficial, such as a few daily walks up and down the stairs. In one Canadian study people exercising three times a week were 40 per cent less likely to develop Alzheimer's disease.
- maintaining normal **blood pressure**
- keeping **cholesterol** levels at normal levels



- **an active social life** - including interactive and especially organized social leisure activities, for example playing cards, group theatre-going.
- **intellectual activity** - the "use it or lose it" principle, such as doing crossword puzzles, reading, playing chess, and so on.
- **protecting your head**, especially by wearing safety helmets during recreation and sporting activities to reduce traumatic head injury
- **hormone replacement therapy (HRT)** - despite a recent large-scale clinical study on women which recommended discontinuation of HRT because it was both ineffective and had potentially dangerous side effects, a number of clinical researchers continue to regard it as worthy of further study. Time will tell.

Adopting a lifestyle that ignores risk factors does not mean one will develop Alzheimer's disease, but it does increase the odds.



Brain changes that occur with Alzheimer's disease

(i) Alzheimer "plaques and tangles"

The plaques.

These are made largely of a protein called "beta amyloid", or "A-beta", which is actually split off from a much larger protein molecule known as "APP". Both APP and A-beta are present in normal brains, but their function is still under investigation. The key problem in Alzheimer's disease is that abnormally high amounts of A-beta accumulate in the brain, overwhelming the enzymes and other molecules whose job it is to clear it away. As well as an increased production of A-beta, the clearing away process itself appears to be defective. It is now accepted that the real danger comes when the individual A-beta molecules clump together to form small toxic aggregates; in fact, the damage to the brain seems mostly to have been done by the time these aggregates stick together and then deposit out to form the recognizable amyloid plaques.

The tangles.

These are made of a protein called tau, which, like amyloid, occurs in normal nerve cells, but in Alzheimer's disease it becomes chemically altered and piles up as thread-like tangles impairing tau's key roles in nerve cells. One of these roles is in nerve sprouting, an important feature of self-repair in the nervous system (see page 10). Another tau role

is in maintaining a kind of railway track system inside nerve cells that moves needed chemicals and tiny organelles up and down the nerve fibres between the cell body and the distant nerve endings. The cell body is the factory and powerhouse for the entire nerve cell. This transport system is essential for the cell to work and survive, and the tangles disrupt it: in a sense they choke the cells to death. The first casualties of disrupted transport are the nerve endings, which contact the next cells in the circuit. They're vulnerable because they're so far away from their cell bodies, the source of their nutrients. Consequently the earliest signs of disturbed nerve cell function are seen at these junctions (called "synapses"), and in animal models of Alzheimer's disease it is here that researchers focus to see if future therapies are proving successful.

A controversy.

Many researchers believe that the amyloid deposits not only make the nerve cells sick, but they somehow promote the development of tangles, and it is probably these that actually kill the nerve cells. In keeping with this "cascade hypothesis", when mice models of Alzheimer's disease (these are explained on page 8) were immunized against A-beta, not only the plaques but the tangles tended to disappear. Moreover tangles generally appear after the plaques have developed. In any event both plaques and tangles are definitely implicated in Alzheimer's disease. However, the situation is complicated. The brains of some entirely normal elderly people have been found to have as many amyloid plaques as in Alzheimer brains, but with no dementia! The fact is, however, that most researchers still regard A-beta as the main threat, and still direct their efforts to eliminating it.

(ii) Inflammation of the brain

Whenever and wherever the body suffers trauma, or is attacked by some kind of potentially threatening influence such as an infection or a toxin, it defends itself in part by mounting an inflammatory response. This, which is actually an immune response, also occurs in the Alzheimer brain. Unfortunately the disease challenge is so great that the response becomes excessive, and instead of helping it actually worsens the situation. Some of the normally protective substances produced by the brain's immune cells actually promote death of cells.

(iii) Shrinkage and degeneration of nerve cells

This process, which first begins in the part of the brain that deals with thinking and memory, is progressive, eventually affecting all parts of the brain which consequently shrinks. The shrinkage is most marked, however, in the thinking and memory regions, and this is very readily seen by brain imaging.

Drug treatments

(i) Aricept™ (donepezil), Exelon™ (rivastigmine) and Reminyl™ (galantamine)

These drugs are “cholinesterase inhibitors”. They help preserve the ability of sick nerve endings to transmit the nerve messages to the next cell in the chain. The first of these drugs appeared in 1986, but wasn’t consistently effective until ten years later when along came the new generation of cholinesterase inhibitors, and their success was rapidly recognized.

How they work makes a fascinating story. Nerve messages, or impulses, travel along nerve fibres by an electrical mechanism, but the electricity is inadequate to cross the junctions between the nerve and the next cell. Nature invented a mechanism to deal with this problem: each arriving impulse releases a tiny blip of a chemical called a “neurotransmitter”, which diffuses very rapidly across the junction to stimulate the next cell. For Alzheimer’s disease the most important neurotransmitter is “acetylcholine”, the one used by the nerve cells in the thinking and memory-making parts of the brain. After the acetylcholine has carried the message across the junction it’s critical that it be

eliminated immediately, otherwise it would keep on stimulating the downstream cell. This could be disastrous, leading to seizures for example. Nature dealt with this potential danger by ensuring that the acetylcholine is destroyed immediately after it’s delivered the message, and this is done by an enzyme called cholinesterase.

Now, in Alzheimer’s disease the blip of acetylcholine that is released by each arriving nerve impulse gets progressively smaller and smaller as the nerve endings get sicker and sicker, eventually becoming too small to transmit the message across the junction. Cholinesterase inhibitors prevent cholinesterase from destroying acetylcholine, and thus what little acetylcholine is released is preserved, building up to levels high enough to get the message across to the next cell. And it works! However, eventually the sick nerve endings begin to degenerate, and they fall away from the junctions and messages can no longer be transferred across them. To reach this point takes usually from two to three years (but sometimes much longer), which is why cholinesterase inhibitors usually work best in the short term.

The consensus remains that, though not a cure, cholinesterase inhibitors are of benefit to at least a significant proportion of those with diagnosed Alzheimer’s disease, though there is indeed an unexplained variation among individuals as to how well they respond. Remarkably, in some instances cholinesterase inhibitors seem to have been effective for as long as eight to 10 years, and new research is suggesting that another of their actions is somehow to protect nerve cells from toxic influences, which include the plaques and tangles and to do this even when the Alzheimer’s disease is well advanced. A promising development discussed later is the use of cholinesterase inhibitors in combination with other drugs like Ebixa (see page 8).

When taken orally, many cholinesterase inhibitors unfortunately can cause gastrointestinal issues as a side effect. To avoid this side effect one drug company is trying a new method. The drug (Exelon™) is not swallowed but is contained in a skin patch from which it is absorbed directly into the body. Although there are problems such as knowing the exact dosage being taken in, this approach could offer substantial promise for eliminating the side effects of cholinesterase inhibitors.



(ii) Ebixa® (memantine hydrochloride)

This story has to start by talking about another neurotransmitter called “glutamate”. Unlike acetylcholine, glutamate is not destroyed by an enzyme after doing its job of conveying the message across the junctions between nerve cells. Instead it’s taken back up into the nerve endings from which it was released, in other words, it’s recycled. This uptake requires that the glutamate combines first with special receiving molecules on the nerve endings called glutamate receptors (known as “NMDA receptors”). However, there’s a twist to the story here. All the cells of the body contain a lot of glutamate because it has important metabolic roles aside from being a neurotransmitter. When cells get sick, especially nerve cells, glutamate leaks out, and its concentrations outside the sick nerve cells can be so high that the increased amount that’s taken back by way of the glutamate receptors is toxic, and indeed quite deadly. This is one of the reasons nerve cells die in Alzheimer’s disease – their sickness could be initially mild, but the massive glutamate leakage and re-uptake multiplies the threat.

Memantine acts by blocking the glutamate receptors and preventing the re-uptake of the glutamate into the nerve

endings. The beauty of this approach is that enough glutamate gets back into the sick nerve endings to be used as a transmitter, but the massive uptake that would be toxic is prevented. Since the glutamate threat develops somewhat late in Alzheimer’s disease, memantine stands as one treatment that can be effective at moderate to advanced stages of the disease. And there is better news: ongoing research is finding that combining cholinesterase inhibitors together with memantine seems to greatly improve the outcome, more than predicted from the sum of the effects of either drug alone. This “combination therapy” seems likely to become an exciting therapeutic approach in the future.

What other leads are being followed that could lead to earlier diagnosis or new treatments?

(i) Vaccines

There are promising developments here. Vaccines became a real possibility when animal models of Alzheimer’s disease were created (that is, genetic engineering was used to get the genes for familial Alzheimer’s disease into mice). The brains of these mice develop amyloid plaques and the mice are memory-impaired.

Researchers then designed a modified A-beta which, when it was injected into the mice, induced their immune systems to make antibodies against it. Because the modified A-beta was so like the normal A-beta, the antibodies also worked against the A-beta already in the brain, and the result was a significant reduction of the plaques and an improvement in the cognitive abilities of the mice. Human trials were rapidly undertaken, only to be dramatically stopped in 2002 when some of the participants developed alarming brain inflammation (this didn’t happen with the mice).

So where do we stand? Well, new modified A-beta vaccines are being vigorously sought – and found – that are predicted not to cause brain inflammation. Also, new mouse models are now being produced with “neurofibrillary tangles” in the brain cells, and anti-tangle antibodies are being made and tested. While much remains to be found out, these exciting animal studies are already being extended to human clinical trials, and the early news gives definite hope that within five to seven years there



could well be a vaccination therapy that could revolutionize the treatment of Alzheimer's disease.

(ii) MCI: some important developments relate to “Mild Cognitive Impairment” (MCI), a condition that is being increasingly found in early middle aged and even in young adults. In MCI there is a level of either cognitive and/or memory impairment beyond that expected for normal aging, but not bad enough to be called dementia or Alzheimer's disease. It has been estimated that 85% of people diagnosed with MCI will develop Alzheimer's disease within 10 years so MCI is clearly an important risk factor for the disease. Moreover, brain imaging is showing that abnormal changes almost certainly exist in the brain before MCI is diagnosed, and indeed in some non-MCI people's brains also destined to develop symptoms of Alzheimer's disease. Some researchers believe that abnormal (pathological) changes in the brain like plaques begin as long as 5-10 years before there are signs of dementia. Imaging approaches, added to psychological testing, should make it possible both to pick out the most at-risk MCI individuals, and to assist enormously in the early diagnosis of Alzheimer's disease. This is important: earlier diagnosis means earlier treatment, and the sooner a therapy is started the better. Many clinicians are now recommending that cholinesterase inhibitors be given to people diagnosed with MCI without waiting for signs of Alzheimer's disease to appear.

(iii) Statins: these cholesterol-reducing agents are being investigated because the incidence of Alzheimer's disease appeared to be less for people using these drugs to lower their cholesterol levels. At first it was assumed that the benefit of these statins came from their ability to reduce the incidence of cardiovascular disease (diseases affecting the heart or blood vessels), which is a risk factor for Alzheimer's disease. However, we now know that statins also reduce the production of A-beta from APP, so here is another promising future treatment strategy. Moreover, since cholesterol is a key component of the membranes that enclose nerve cells, abnormal cholesterol levels could seriously alter cell membranes, and thereby alter the responses of nerve cells to substances such as growth factors (see “Promoting brain repair” see page 11), hormones, and of course drugs. Keeping cholesterol from rising above normal levels is clearly very important.



(iv) Alzheimer's disease and diabetes: research on people with Alzheimer's disease and on animal models of the disease is showing that, even when diabetes in the conventional sense is absent, anti-diabetic drugs called “glitazones” can help maintain brain function and, seen in the animal studies and assumed to occur also in people, reduce the development of brain plaques. The continued testing of these drugs is based on the idea that at least a number of people with Alzheimer's disease might actually be suffering from a sort of diabetes of the brain, or what has been suggested to be called “type 3 diabetes”. This idea is supported by the observation that insulin administered through the nasal passage, which can get it preferentially to the brain without going through all the rest of the body, improved memory and cognition in some people – a promise of future therapeutic measures.

(v) Anti-inflammatory agents such as aspirin and other NSAIDs (nonsteroidal anti-inflammatory drugs): Although not yet proven, there is intriguing evidence that people routinely taking anti-inflammatory agents for rheumatic and other conditions are at a decreased risk of getting Alzheimer's disease, and this lead is being followed up. Cannabinoids (cannabis-derived substances) have also been claimed to have anti-inflammatory and other benefits in Alzheimer's disease, but at present the potential dangers associated with their numerous actions in the nervous system make their use problematical.



(vi) Other drug therapies: The news here is very encouraging. Alzhemed™ and Flurizan™ are two examples of new classes of drugs currently in clinical trials and producing promising results. Flurizan and other "secretase inhibitors" work by blocking the process that splits off A-beta from its big parent molecule, APP. This helps to stop the dangerous accumulation of A-beta in the brain. Alzhemed and cyclohexanehexol, another new agent discovered by Toronto researchers, interact with the A-beta molecules as they form, and prevent them from sticking together in small aggregates - aggregates that poison nerve cells and eventually deposit as solid "plaques", but by the time they form most of the damage is already done. Other treatments aim at encouraging the mopping up of the A-beta before it reaches threatening levels. "Ubiquitin" is a naturally-occurring chemical in the brain that helps in this mopping up action, but its levels are reduced in Alzheimer brains. When mice with Alzheimer's disease were given drugs that increased their ubiquitin levels, their brain function improved even when the amyloid plaques

persisted. Presumably this was because the drug prevented the small clumps of amyloid from developing. Iron and other metals have been suggested as risk factors for Alzheimer's disease in certain individuals, and this possibility is being tested in trials of a drug called Clioquinol that helps remove the suspect metals from the body (traces of copper may be needed for amyloid plaques to be produced, but the amounts are virtually impossible to avoid in normal diets). Definitive results are not yet in from these studies. Finally ginkgo biloba, a herbal supplement purported to improve memory, is in clinical trials to see if it affects the onset or severity of Alzheimer's disease.

(vii) Making new nerve cells from stem cells:

Researchers are very excited at the prospect of replacing lost nerve cells in Alzheimer brains by using special cells derived from bone marrow and other tissues, known as "stem cells". These are cells that have not yet reached the stage when they mature into a specific cell type like a nerve cell or a muscle cell, but they can be made to change into nerve cells by appropriate "growth factors" (see page 11). This is usually done before the cells are implanted into the brain. However, in favourable circumstances stem cells have spontaneously converted into nerve cells after they were implanted in the brain, apparently because of the effects of local growth factors and other features of the local environment the stem cells encounter. The stem cell approach is being studied in experimental animals, and in some countries it has already been tested in people with Alzheimer's disease, with ambiguous results. Canada, in common with many other countries, has important limitations on stem cell research, but it seems likely that one day human stem cell trials will become more general after ethically acceptable sources of these cells have been agreed upon, and after effective and safe ways to introduce them into the brain have been worked out. A new and exciting research initiative is focusing on stem cells that occur within the brain itself, trying to encourage them to multiply and migrate to regions where there has been cell damage or loss. There is good evidence that the repair function offered by resident stem cells converting into nerve cells can happen spontaneously after traumatic injury, and even in neurodegenerative conditions like Alzheimer's disease. A practical therapy based on stem cells seems unlikely, however, to appear within the next ten years.

(viii) Promoting brain repair: The special importance of stem cell studies and others now to be mentioned is that they address the problem of brain repair. If the brain functions that are lost in Alzheimer's disease are to be restored, the brain damage must eventually be reversed. Even when a truly successful treatment for Alzheimer's disease appears, i.e. one that actually stops the disease in its tracks so that there's no further brain degeneration, there will still be the need to deal with the damage that's already happened. We have to cure the person as well as the disease! Of great importance here is a class of substances called "growth factors". These substances are nourishing molecules that the body makes continuously throughout life to help maintain the health of all sorts of cells, including nerve cells. One critically important growth factor, the first such to be discovered, is called "nerve growth factor", or NGF for short. NGF is needed especially to keep the nerve cells involved in memory and thinking alive and well. Growth factors also stimulate nerve cells to sprout new branches and make new connections to make up for those lost as neighboring nerve cells die. This "compensatory nerve sprouting" helps recovery after stroke and brain trauma, for example. Unfortunately it doesn't occur so readily in aging, and it is also reduced by some of the known risk factors for Alzheimer's disease. Scientists are



now implanting genetically engineered cells that make NGF into the brains of animal models of Alzheimer's disease, and in one study NGF-producing cells were implanted directly into the brains of people with Alzheimer's disease. Initial results show promise both for keeping nerve cells from dying and in improving cognition.

It is certain that the three approaches, delivery of growth factors, delivery of stem cells, and mobilizing stem cells already resident in the brain, will one day pay off as a way of reversing the damage caused by Alzheimer's disease – but all this will take quite a few years. Another more immediate and quite different way of promoting brain repair is described in the following section.

A proposal: Caregiving could be promoting brain repair

Nerve sprouting from surviving nerve cells is a key feature of repair in the diseased or damaged nervous system. The new sprouts make connections with other surviving nerve cells, compensating for the connections lost when nerve cells died. Nerve sprouting is induced by growth factors among which NGF is very important. However, there is another way to induce nerve sprouting; this is by initiating impulses (nerve messages) in the nerve cells. Experimentally this "driving" as it's called is done either by electrically stimulating the nerve cells, or by increasing the "sensory input", that is by providing increased sensory stimulation such as light, touch, sound, and so on. Now in the parts of the brain that control feeling and thinking, the input that matters most is that from the social environment – from people talking and touching or caressing, physically and emotionally interacting with the individual. This means that the more of this "social stimulation" a person with Alzheimer's disease gets, the more likely it is that their surviving brain cells will be induced to sprout and restore lost connections. Not only that, but research is showing that in mouse models of Alzheimer's disease, "environmental enrichment", which is a form of increased social stimulation, actually reduces the levels of A-beta and the amyloid deposits. The caregiver, family member or anyone else involved with the person with Alzheimer's disease has a critical role here. We should never be put off by absence of immediate response because nerve sprouting and the subsequent making of connections with other nerve

cells can take many months. Now this proposal has obviously not been proven experimentally in humans, but a lot of animal research would support it, and anecdotal accounts from caregivers support it too. The emotional benefits of maintaining contact between people with Alzheimer's disease and their caregivers and family members can only be guessed at, but the bottom line is – keep trying to communicate, keep talking, and keep on showing affection like holding and caressing (without overdoing it of course, which could cause distress to both sides). The thing to avoid at all costs is social isolation.

Social/Psychological Research

The Alzheimer Society Research Program provides equal financial support to Biomedical and Social/Psychological research. The Society and its partners support biomedical research projects in essentially all the areas already discussed in this Research Report. And, while most of the present account focuses on biomedical research, it was felt that the reader would appreciate knowing the range of Society-funded social/psychological research. To this end here is a selection of social/psychological research projects presently or recently funded by the Society.

- Role of home care in dementia care
- Development of an assessment tool for estimating dementia caregiver resources, vulnerabilities and homecare needs
- A process-oriented approach to memory training in older adults in individuals with Mild Cognitive Impairment: Behavioural and preliminary neuroimaging results
- Determining effective cueing strategies used by caregivers with people with Alzheimer's disease
- Day centres and how successful they are in improving quality of life
- How to deal with the issue of using restraints
- How to assess the risks of elderly people living alone
- Do dangerous interactions occur between commonly used herbal and conventional medications?
- Should disturbed sleep in people with Alzheimer's disease be treated differently from that in normal people?
- What technology exists that could assist people with memory problems?
- Can music be a successful source of relaxation for people with Alzheimer's disease?

THE NEXT TEN YEARS

These are going to be even more exciting than the last ten years. Let's look at the developments that seem most likely to pay off in that time. Clinical trials (many already begun and some well advanced) will test the following, and hopefully within the next five to seven years the most promising of them will be approved for people with Alzheimer's disease:

1. Drugs that block the enzymes that split off the toxic A-beta from APP.
2. Drugs that prevent the threatening clumping together of newly formed A-beta molecules.
3. Drugs that help clear away the accumulating A-beta molecules before they begin clumping together.
4. "Neuroprotective" drugs that increase the ability of threatened nerve cells to stay alive.
5. Drugs that will prevent the chemical modification of tau protein and so prevent tangles.
6. New vaccines that will eliminate amyloid but not have the dangerous side effects of the first vaccines.
7. New vaccines that will eliminate tangles.
8. Improved techniques to implant genetically engineered living cells into the brain for delivery of growth factors and other drugs.
9. New anti-diabetic drugs that will correct glucose metabolism in the brains of people with Alzheimer's disease and counteract the development of plaques and tangles.
10. New drug delivery techniques which will ensure that drugs get to the regions of the brain where they are needed.
11. Improved non-invasive imaging techniques that will reveal plaques and tangles even before dementia develops, facilitating early diagnosis and revealing whether treatment strategies are reducing the brain abnormalities.
12. New approaches to measure amyloid in the blood and in the cerebrospinal fluid (CSF) to help in early diagnosis, and in evaluation of treatment therapies.
13. Early diagnosis based on the pattern of brain waves (EEG).
14. Early diagnosis based on chemical changes in the skin and in urine.
15. New cognitive training regimens that will help slow down the decline in brain functioning without the use of drugs.



The Researchers

Biomedical researchers try to understand exactly how adverse changes are triggered and maintained in the Alzheimer brain, and are trying to design treatments to prevent their development. As well, they are actively following a variety of approaches to promote brain repair.

Social and psychological researchers, including health professionals such as nurses, try first to identify the personal, social and environmental factors that affect the quality of life of the person with Alzheimer's disease and of their caregivers, and then they try to improve these.

Clinical researchers (these are represented in both of the two preceding groups) extend the studies of the laboratory scientists to humans, for example by carrying out trials of new drugs and other therapeutic approaches. They also participate in brain imaging that both confirms diagnosis and adds to the evaluation of treatment, and they work with other health-care professionals to improve the person's quality of life.

Finally, all the researchers involved in Alzheimer's disease help solve the ethical issues especially to do with "informed consent" and with privacy concerns in genetic testing.

Where does the Alzheimer Society come in?

The Alzheimer Society is a leading funder of Alzheimer research and research training in Canada. In 2006, the Society (with our partners) funded 24 new grants and training awards, amounting to almost \$3 million. The funding for the research program comes from provincial and local Alzheimer Societies across Canada, and from the generosity of individuals and corporations. The Alzheimer Society of Canada (ASC) administers the research program. The research applications received for the annual competition are reviewed through an extensive peer review process, and the funding is divided equally between the biomedical and the social/psychological fields. Canadian scientists rank among the top Alzheimer scientists in the world. ASC seeks out partnerships to enhance the impact of its research funding. Our current partners include:

- Provincial Alzheimer Societies and local Chapters across Canada
- Canadian Institutes of Health Research (CIHR)
- Canadian Nurses Foundation (CNF)
- Heart and Stroke Foundation (HSF)
- Pfizer Canada Inc.
- Institute of Aging (CIHR)
- Institute of Gender and Health (CIHR)
- Fonds de la recherche en santé du Québec (FRSQ)
- Alzheimer Society Of Saskatchewan (supports Young Investigator Grants)

ASC and its partners support biomedical and social and psychological research projects in essentially all the areas discussed in this Research Report.

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